FILE 'REGISTRY' ENTERED AT 12:34:33 ON 10 DEC 2003

L1	1	S	SARIN/CN
L2	1	S	TABUN/CN
L3	1	S	SOMAN/CN
L4	1	S	ROCURONIUM/CN
L5	0	S	MIVACURIAM/CN
L6	1	S	SUXAMETHONIUM/CN
L7	2	S	TUBOCURARINE/CN

FILE 'CAPLUS' ENTERED AT 12:37:44 ON 10 DEC 2003

L8	5204	S	TUBOCURARINE
L9	17853	S	NEUROMUSCULAR
L10	244441	S	BLOCK
L11	259962	S	L9 OR L10
L12	1864	S	L8 AND L11
L13	24852	S	CYCLODEXTRIN
L14	2	S	L12 AND L13
L15	1296	S	SARIN
L16	482	S	TABUN
L17	1950	S	SOMAN
L18	1903	S	VX
L19	4289	S	L15 OR L16 OR L17 OR L18
L20	180	S	L19 AND L11
L21	946	S	NEUROMUSCULAR BLOCK
L22	15	S	L20 AND L21
L23	2976610	S	TREAT?
L24	217738	S	THERAPY
L25	5743	S	ANTIDOTE
L26	3083803	S	L23 OR L24 OR L25
L27	80	S	(L20 NOT L26) NOT L22
L28	1	S	2001:417024/AN
L29	515774	S	REVERS?
L30	16	S	L29 AND L27
L31	1954	S	?CURONIUM
L32	0	S	SUXMETHONIUM
L33	6816	S	L8 OR L31
L34	440	S	L33 AND L11 AND L29
L35	98	S	L34 AND L21
L36	26	S	REVERSAL/TI AND L35

L22 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:525993 CAPLUS
DOCUMENT NUMBER: 122:281225
TITLE: The electrophysiological study of neuromuscular block induced by soman
AUTHOR(S): Ji, Zhanxin
CORPORATE SOURCE: Beijing Inst. Toxicol. Pharmacol., Beijing, 100850, Peop. Rep. China
SOURCE: Shengli Kexue Jinzhan (1994), 25(4), 333-5
CODEN: SLKHA8; ISSN: 0559-7765
PUBLISHER: Zhongguo Shengli Xuehui
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review, with 11 refs., of the electrophysiol. study of neuromuscular block by intoxication with the cholinesterase inhibitor soman.

L22 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:317513 CAPLUS
DOCUMENT NUMBER: 120:317513
TITLE: Treatment of tabun poisoned guinea-pigs with atropine, HLoe 7 or HI 6: effect on respiratory and circulatory function
AUTHOR(S): Worek, Franz; Kirchner, Thomas; Szinicz, Ladislaus
CORPORATE SOURCE: Inst. Pharmakol. Toxikol., Akad. Sanit., Garching, 85748, Germany
SOURCE: Archives of Toxicology (1994), 68(4), 231-9
CODEN: ARTODN; ISSN: 0340-5761
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The therapeutic efficacy of HLoe 7, HI 6 and obidoxime (with and without atropine) was compared in tabun poisoned guinea-pigs. In addn., the therapeutic effect of atropine in guinea-pigs poisoned by various doses of tabun was investigated. Female Pirbright-white guinea-pigs were anesthetized with urethane (1.8 g/kg) and the carotid artery, jugular vein and trachea were cannulated. After baseline measurements the animals received tabun, 60, 180 or 300 .mu.g/kg, and 2 min later the antidotes (all i.v.): obidoxime, HLoe 7, or HI 6 (30 or 100 .mu.mol/kg, each) or atropine (10 mg/kg) or a combination of atropine and one of the oximes. Respiratory and circulatory parameters were recorded for 60 min or until the death of the animal. Erythrocyte, brain and diaphragm AChE activity was detd. in every animal after the expt. Poisoning by tabun resulted in a rapid deterioration of respiratory function and respiratory arrest within 5 min. Atropine treatment was very effective in improving the respiratory function after tabun 60 .mu.g/kg but was ineffective after tabun 300 .mu.g/kg. However, circulatory parameters were restored almost completely in all atropine therapy groups. Therapy of tabun 300 .mu.g/kg poisoned animals with atropine plus oxime (30 .mu.mol/kg) improved respiration to a variable extent and restored circulation. The efficacy decreased in the order obidoxime > HLoe 7 .mchgt. HI 6. Use of oximes 100 .mu.mol/kg did not further increase the therapeutic effect. Oximes alone were completely ineffective. The considerable therapeutic efficacy of atropine and oximes was not accompanied by a reactivation of diaphragm or brain AChE. Erythrocyte AChE was partially reactivated by obidoxime. Tabun primarily impaired central respiratory control, but peripheral neuromuscular block developed already at low tabun doses. Atropine was very effective in restoring circulation but respiration was improved only after low doses of tabun. The results of this investigation demonstrate a considerable effect of atropine plus obidoxime or HLoe 7 in improving respiration and circulation after high dose tabun. This effect was not accompanied by a noticeable AChE reactivation, indicating the involvement of some other "direct" mechanisms. HLoe 7 has to be considered as a broad-spectrum antidote, being superior to obidoxime or HI 6.

L22 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:71094 CAPLUS
DOCUMENT NUMBER: 120:71094
TITLE: Analysis of cardiovascular and respiratory effects of various doses of soman in guinea pigs: efficacy of atropine treatment
AUTHOR(S): Worek, F.; Szinicz, L.
CORPORATE SOURCE: Inst. Pharmacol. Toxicol., Federal Armed Forces Med. Acad., Garching, D-85748, Germany
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1993), 325, 96-112

CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The results of this study suggest that the soman-induced respiratory depression is primarily caused at the central nervous level and that a significant peripheral neuromuscular block develops only at very high soman doses. The circulatory disturbances are mainly the result of bradycardia due to peripheral muscarinic stimulation. Atropine has a high therapeutic effect in the restoration of circulatory function and may even improve respiration at high soman doses.

L22 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1983:553392 CAPLUS
DOCUMENT NUMBER: 99:153392
TITLE: The reversal by oximes and their deoximinomethyl analogs of neuromuscular block produced by soman
AUTHOR(S): French, Mary C.; Wetherell, Janet R.; White, Phillip D. T.
CORPORATE SOURCE: Chem. Def. Establ., Minist. Def., Salisbury/Wiltshire, SP4 0JQ, UK
SOURCE: European Journal of Pharmacology (1983), 91(4), 399-409
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of oximes and related compds. were assessed for their ability to restore soman [96-64-0]-induced neuromuscular block in the isolated diaphragm prepn. of the rat, guinea pig, and marmoset. In the rat, the bispyridinium oximes HS6 (I) [22625-23-6], HI6 [34433-31-3], and HS14 [34211-28-4] were superior to P2S [154-97-2] and all other compds. tested. Conversely, in the guinea pig, most of the compds. tested produced a good reversal of neuromuscular block. In a limited no. of expts. in the marmoset, only a partial reversal of neuromuscular block was obtained with the oximes HI6 and I. The restoration of neuromuscular block was due to .gtoreq.1 of the following factors: (1) enzyme reactivation, (2) direct action, and (3) adaptation. Apparently, both the acetylcholine receptor and the rate of aging of soman-inhibited acetylcholine esterase [9000-81-1] are different in these 3 species.

L22 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1979:569488 CAPLUS
DOCUMENT NUMBER: 91:169488
TITLE: The reversal by pyridostigmine of neuromuscular block produced by soman
AUTHOR(S): French, Mary C.; Wetherell, Janet R.; White, P. D. T.
CORPORATE SOURCE: Chem. Def. Establ., Minist. Def., Salisbury, UK
SOURCE: Journal of Pharmacy and Pharmacology (1979), 31(5), 290-4
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the isolated phrenic nerve-diaphragm prepn. of the rat or guinea pig, soman [96-64-0] (40 or 100 nM) produced an irreversible redn. in tetanic tension and functional acetylcholinesterase (EC 3.1.1.7) (I) [9000-81-1] activity. Pretreatment with pyridostigmine (II) [155-97-5] (1 .times. 10-7 to 1 .times. 10-9M), followed by removal of I, produced a return of tetanic tension and a 5% increase in functional I activity. Thus, II pretreatment may protect the neuromuscular junction from irreversible block by soman, by carbamoylating a portion of the I. After removal of excess soman spontaneous decarbamoylation produced sufficient free I to restore neuromuscular function.

L22 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1969:448061 CAPLUS
DOCUMENT NUMBER: 71:48061
TITLE: Effect of Toxoqonin on the neuromuscular block caused by an anticholinesterase (Soman)
AUTHOR(S): Angelov, A. D.
CORPORATE SOURCE: Vissh Voennomed. Inst., Bulg.
SOURCE: Eksperimentalna Meditsina i Morfologiya (1969), 8(1), 51-5
CODEN: EKMMA8; ISSN: 0367-0643
DOCUMENT TYPE: Journal
LANGUAGE: Bulgarian

AB In expts. on the cat ischiadic-gastrocnemius and the rabbit phrenic-diaphragm **neuromuscular** prepns. in vivo, it was shown that the **neuromuscular block** induced by **Soman** (15-60 .gamma./kg., i.v.) was completely antagonized by toxogonin in doses of 8-20 mg./kg., i.v.

L22 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1967:84455 CAPLUS
DOCUMENT NUMBER: 66:84455
TITLE: Effects of an organic phosphate on the responses of denervated muscle to acetylcholine and some **neuromuscular** blocking agents
AUTHOR(S): Loomis, Ted A.; Konker, A. C.
CORPORATE SOURCE: Sch. of Med., Univ. of Washington, Seattle, WA, USA
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1967), 165(2), 308-18
CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acetylcholine chloride (I) (0.001-10 .gamma./kg.) injected i.v. into atropinized rats induced contracture in denervated anterior tibial muscle. Sensitivity of the muscle to I was max. 1-3 weeks after denervation. Pretreatment of the animals with **soman** (90 .gamma./kg.) increased the sensitivity of the muscle to I. d-Tubocurarine (25 .gamma./kg.) injected i.v. produced a contracture similar to, but of longer duration than, that induced by injection of I. Following depletion of cholinesterase (II) by **soman** (50-90 .gamma./kg.), administration of d-tubocurarine produced a contracture in the denervated muscle which was of similar amplitude but of 4-fold increased duration, compared with the response obtained prior to administration of **soman**. When d-tubocurarine was administered to the II-depleted animal during an I-induced contracture of the denervated muscle, an additive response was obtained. I.v. injections of histamine (5 .gamma./kg.), decamethonium (5 .gamma./kg.), or succinylcholine (1-2 .gamma./kg.) induced a contracture in the denervated muscle prepn. following doses which were insufficient to produce a **neuromuscular block** in the innervated muscle. Following an injection of **soman** (50-90 .gamma./kg.), decamethonium or histamine induced a contracture of similar amplitude and duration to that obtained following control injections of these drugs prior to depletion of II.

L22 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1963:62003 CAPLUS
DOCUMENT NUMBER: 58:62003
ORIGINAL REFERENCE NO.: 58:10630f-g
TITLE: Reversal of effects on the rat nerve-diaphragm preparation produced by methylfluorophosphorylcholines
AUTHOR(S): Fredriksson, T.; Tibbling, G.
CORPORATE SOURCE: Research Inst. Natl. Defense, Sundbyberg, Swed.
SOURCE: Biochemical Pharmacology (1959), 2, 63-7
From: Biol. Abstr. 36, Abstr. No. 20384(1961).
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The effects of 4 organophosphorylcholines [methylfluorophosphorylcholine, methylfluorophosphoryl-.beta.-methylcholine, methylfluorophosphorylhomocholine, and methylflnorophosphorylcarbocholine (3,3-dimethylbutoxyphosphoryl fluoride)] and methylisopropoxyphosphoryl fluoride (**sarin**) on the rat nerve-diaphragm prepn. were studied together with the reversal of these effects by various reactivators (2-PAM, MINA, DINA). **Sarin** and the carbocholine analog produced **neuromuscular block** more rapidly than did the quaternary N compds. The **neuromuscular block** produced by satin was the easiest to reverse; the reactivators had less effect on the **block** produced by the organophosphorylcholines, particularly in the case of the homocholine analog.

L22 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1961:34119 CAPLUS
DOCUMENT NUMBER: 55:34119
ORIGINAL REFERENCE NO.: 55:6693b-e
TITLE: Effects of 1,1'-trimethylenebis(4-formylpyridinium bromide) dioxime (TMB-4) on cholinesterase activity and **neuromuscular block** following poisoning with **sarin** and diisopropyl phosphofluoridate (DFP)
AUTHOR(S): Fleisher, Joseph H.; Hansa, John; Killos, Paul J.; Harrison, Charles S.
CORPORATE SOURCE: Army Chem. Center, MD
SOURCE: Journal of Pharmacology and Experimental Therapeutics

(1960), 130, 461-8
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. CA 54, 15683h; Federation Proc. 18, 227 (1959). Neuromuscular blockade from poisoning of rats with DFP is rapidly antagonized by TMB-4 in vitro and in vivo. Concurrent study of the cholinesterase (ChE) activity after addn. of TMB-4 in vitro showed significant recovery of ChE activity of intact muscle after 10 min. under the exptl. conditions employed. Comparable results were obtained by TMB-4 treatment of sarin-poisoned rats. No reactivation of brain ChE activity was found following TMB-4 treatment; this is consistent with the apparent inability of quaternary ammonium compds. to penetrate the blood-brain barrier and the potentiating action of atropine in promoting the chemotherapeutic effectiveness of TMB-4 shown previously.

L22 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1958:41803 CAPLUS
DOCUMENT NUMBER: 52:41803
ORIGINAL REFERENCE NO.: 52:7533i,7534a
TITLE: Reversal by oximes of neuromuscular block produced by anticholinesterases
AUTHOR(S): Holmes, R.; Robins, E. L.
CORPORATE SOURCE: Chem. Defence Exptl. Estab., Porton, UK
SOURCE: British Journal of Pharmacology and Chemotherapy (1955), 10, 490-5
CODEN: BJPCAL; ISSN: 0366-0826
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Wedensky block in the isolated rat phrenic nerve-diaphragm prepn. induced by tetraethyl pyrophosphate (I), diisopropyl phosphorofluoridate (II), or sarin was rapidly reversed by diisonitrosoacetone and monoisonitrosoacetone. Pyridine-2-aldoxime methiodide reversed block due to anticholinesterases and itself caused neuromuscular block at higher concns. In rat gracilis muscle in vivo, II caused an increase in conduction velocity, which was restored to normal by oximes. Block in the cat tibialis muscle due to intravenous I or sarin was slowly reversed by oximes. The oximes did not reverse block caused by d-tubocurarine, succinylcholine, or decamethonium, and they had a direct toxic action on muscle.

L22 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1958:2798 CAPLUS
DOCUMENT NUMBER: 52:2798
ORIGINAL REFERENCE NO.: 52:567b-c
TITLE: Pyridine-2-aldoxime methiodide in the treatment of sarin and tabun poisoning, with notes on its pharmacology
AUTHOR(S): Brown, Robert V.; Kunkel, Anne M.; Somers, Lea M.; Wills, J. Henry
CORPORATE SOURCE: Army Chem. Center, MD
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1957), 120, 276-84
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Sarin and tabun kill primarily by direct central respiratory paralysis. Both produce neuromuscular block in the cat; recovery is moderately rapid after sarin, slow after tabun. In the dog both agents augment twitch height but block sustained tetanus. Prophylactic administration of atropine sulfate conferred little respiratory protection in the cat and only moderate protection in the dog. Pyridine-2-aldoxime methiodide, 5 mg./kg. intravenously, is an effective and safe adjunct to atropine sulfate in the therapy of sarin or tabun poisoning; by itself it is a mediocre antidote.

L22 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1957:6726 CAPLUS
DOCUMENT NUMBER: 51:6726
ORIGINAL REFERENCE NO.: 51:1456g-i
TITLE: Antagonists to the neuromuscular block produced by Sarin
AUTHOR(S): Kunkel, A. M.; Wills, J. H.; Monier, J. S.
CORPORATE SOURCE: Army Chem. Center, MD
SOURCE: Proc. Soc. Exptl. Biol. Med. (1956), 92, 529-32
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Large intravenous doses of Sarin decrease the twitch height of

the cat gastrocnemius-soleus muscle group excited by maximal elec. stimulation of the sciatic nerve at 2-sec. intervals. Various compds. contg. quaternary N atoms, including several atropine derivs., overcome the decrease in twitch height. Some compds. with significant anticholinesterase activity enhance the **Sarin**-induced decrease in twitch height despite the abolition by **Sarin** of demonstrable cholinesterase activity in the muscle.

L22 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1955:13041 CAPLUS
DOCUMENT NUMBER: 49:13041
ORIGINAL REFERENCE NO.: 49:2616h-i,2617a
TITLE: Analysis of the central and peripheral components of respiratory failure produced by anticholinesterase poisoning in the rabbit
AUTHOR(S): Wright, P. G.
CORPORATE SOURCE: Univ. Coll., London
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (1954), 126, 52-70
CODEN: JPHYA7; ISSN: 0022-3751
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Intravenous administration of tetraethyl pyrophosphate (30-40 .gamma./kg.) or isopropyl methyl phosphonofluoride (**Sarin**) (400-450 .gamma./kg.) produced respiratory failure in anesthetized rabbits. This involved **neuromuscular block**, central depression, and increased resistance to lung inflation, in urethan-anesthestized animals. Atropine (I) or hyoscine (II) in 2 mg./kg. doses did not remove **neuromuscular block** from either type of anticholinesterase (III) used, but restored previously lost discharge in fibers of the phrenic nerve, provided that degree of asphyxia was not extreme. Pretreatment with I or II prevented central failure by III, unless **neuromuscular block** depressed respiration to a point of severe asphyxia; at that point artificial respiration restored the activity of such centers.

L22 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1954:22732 CAPLUS
DOCUMENT NUMBER: 48:22732
ORIGINAL REFERENCE NO.: 48:4120d-f
TITLE: The failure of respiration in death by anticholinesterase poisoning
AUTHOR(S): De Candole, C. A.; Douglas, W. W.; Evans, C. Lovatt; Holmes, R.; Spencer, K. E. V.; Torrance, R. W.; Wilson, K. M.
CORPORATE SOURCE: Chem. Defence Exptl. Establishment, Porton, UK
SOURCE: British Journal of Pharmacology and Chemotherapy (1953), 8, 466-75
CODEN: BJPCAL; ISSN: 0366-0826
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The various anticholinesterase drugs (E600, diisopropyl fluophosphate, **tabun**, **sarin**, **soman**, and TEPP) which produce respiratory failure in mammals do so in 3 main ways: by producing bronchoconstriction, by **neuromuscular block**, and by central respiratory failure. Central failure was the predominant factor in most instances but the detailed picture varied with the species, the drug used, and the dose administered. Depression of activity of the respiratory center was due to a direct central nervous system action. Atropine protected against central inhibition and broncho-constriction, while artificial ventilation protected in the presence of neuro-muscular blockade.

L22 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1954:8340 CAPLUS
DOCUMENT NUMBER: 48:8340
ORIGINAL REFERENCE NO.: 48:1570i,1571a-b
TITLE: Poisoning with anticholinesterases. The physiological mechanism involved in poisoning with anticholinesterases
AUTHOR(S): Holmes, R.
CORPORATE SOURCE: Ministry Supply, London
SOURCE: Proc. Roy. Soc. Med. (1953), 46, 799-800
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB TEPP(tetraethyl pyrophosphate), DFP(diisopropyl fluophosphate), E600(Paraoxon), **Sarin**, and **Tabun** potentiate the postganglionic parasympathetic activity and produce miosis, salivation, rhinorrhea, and lacrimation. Bronchoconstriction (I) and a slowdown of the heart are the result of potentiated vagal activity. Peristalsis is

increased and Wedensky's neuromuscular block (II)
occurs. The violent convulsions and inhibitions of the inspiratory center (III) are central nervous effects of the poisoning. Inhibition of respiration causes the death of rabbits, cats, and monkeys but there are large species differences. I is not severe in rabbits, death is caused by III, not by II. I but not II is severe in cats, while neither I nor II is severe in monkeys.

L30 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:380460 CAPLUS
DOCUMENT NUMBER: 125:51091
TITLE: Single fiber electromyographic changes in man after organophosphate exposure
AUTHOR(S): Baker, D. J.; Sedgwick, E. Michael
CORPORATE SOURCE: Southampton General Hospital, University Southampton, Southampton, S016 6YD, UK
SOURCE: Human & Experimental Toxicology (1996), 15(5), 369-375
CODEN: HETOEA; ISSN: 0960-3271
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neuromuscular (NM) changes resulting from organophosphate exposure are known to be complex. After severe acute poisoning recovery from initial depolarization paralysis may be followed in a limited no. of cases by onset of a non-depolarization paralysis (the Intermediate Syndrome). It is not clear whether this block arises subclinically in all cases of poisoning as a sequel to the initial depolarization. Single fiber electromyog. (SFEMG) is a sensitive clin. neurophysiol. technique allowing detection of subclin. changes at the neuromuscular junction. In the study reported it has been used to examine changes in NM transmission in the forearm of fit volunteers exposed to a low level of sarin (iso-Pr Me phosphonofluoridate). Small changes in SFEMG were seen at three hours and three days after an exposure sufficient to cause a redn. in red cell acetyl cholinesterase to 60% of normal. The SFEMG changes were not accompanied by any clin. neuromuscular symptoms or signs and returned to normal 2 yr after exposure. The results indicate that there are reversible subclin. changes compatible with the development of non-depolarizing NM block without frank clin. expression. In the small population examd. there were individual variations in response which may reflect differences in safety margin at the neuromuscular junction.

L30 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:210262 CAPLUS
DOCUMENT NUMBER: 120:210262
TITLE: Contribution of direct actions of the oxime HI-6 in reversing soman-induced muscle weakness in the rat diaphragm
AUTHOR(S): Adler, Michael; Maxwell, Donald M.; Filbert, Margaret G.; Deshpande, Sharad S.
CORPORATE SOURCE: Neurotoxicol. Branch., US Army Med. Res. Inst. Chem. Def., Aberdeen Proving Ground, MD, 21010, USA
SOURCE: European Journal of Pharmacology, Environmental Toxicology and Pharmacology Section (1994), 270(1), 9-16
CODEN: EPEPEG; ISSN: 0926-6917
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The actions of the bispyridinium oxime HI-6 ([[[(4-aminocarbonyl)pyridino]methoxy]methyl]-2-[(hydroxyimino)methyl]pyridinium dichloride) were investigated in vitro on rat phrenic nerve-hemidiaphragm prepns. Isometric twitch and tetanic tensions were elicited at 37.degree.C with supramaximal nerve stimulation at frequencies of 20 and 50 Hz. To approx. normal respiration patterns, trials consisting of 30 successive 0.55 s trains were alternated with 1.25 s rest periods. Under control conditions, the above stimulation pattern generated tensions that were well maintained at both frequencies. In contrast, a marked depression of muscle tension was obsd. in diaphragms removed from rats administered 339 .mu.g/kg soman (3 LD50) and tested in vitro. Addn. of HI-6, 4 h after soman exposure, led to a nearly complete recovery of muscle tension at 20 Hz. At 50 Hz, muscle tensions still declined esp. when trains were elicited at 1.25 and 3 s intervals. The recovery of HI-6 obsd. in this study appears to be mediated by mechanisms unrelated to acetylcholinesterase reactivation since no increase of enzymic activity was detected and the effect was reversed by a brief washout in oxime-free phsiol. soln. The results suggest that the direct action of HI-6 may play a role in restoring soman-induced diaphragmatic failure but this effect would be significant primarily under low use conditions.

L30 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:553603 CAPLUS
DOCUMENT NUMBER: 119:153603
TITLE: Biphasic action of sarin on monosynaptic reflex in the neonatal rat spinal cord in vitro
AUTHOR(S): Warnick, J. E.; Deshpande, S. B.; Yang, Q. Z.; Das

Gupta, S.
CORPORATE SOURCE: Sch. Med., Univ. Maryland, Baltimore, MD, 21201, USA
SOURCE: Archives of Toxicology (1993), 67(5), 302-6
CODEN: ARTODN; ISSN: 0340-5761
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The action of sarin, an organophosphorus (OP) compd., was examd. in vitro for its effects on the spinal monosynaptic reflex (MSR) in neonatal rats. The effects of sarin were biphasic, i.e. facilitation at lower concns. (2-20 nM) followed by depression of the MSR at concns. above 30 nM. Facilitation of MSR was maximal (150% of control) at 20 nM sarin. The depression of MSR was maximal (70% of control) at 200 nM sarin, with half maximal inhibition occurring at 90 nM sarin. Atropine (200-500 nM) effectively reversed the depression caused by sarin, while pretreatment with low concns. of atropine (10 nM) completely blocked the depression otherwise obsd. with sarin. Benactyzine was also effective in preventing sarin-induced depression, while pirenzepine was less effective. The nicotinic blocking agents tubocurarine and mecamylamine were, however, ineffective in preventing or reversing sarin-induced depression. The facilitation of MSR seen with lower concns. (2-20 nM) correlated well with the blockade of late phase inhibition (between 30 and 50 ms conditioning-test interval) elicited in spinal cord by stimulating the adjacent dorsal root at various condition-test intervals, which has been shown elsewhere to be sensitive to bicuculline (Deshpande and Warnick, 1988). Thus, it is speculated that sarin at lower concns. blocks GABA transmission, producing facilitation, and at higher concns. activates the muscarinic receptors producing depression of MSR. The beneficial action of pretreatment with antimuscarinic agents may be attributed to the protection of the muscarinic receptors.

L30 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:249523 CAPLUS
DOCUMENT NUMBER: 118:249523
TITLE: Ion channel blockade by oximes and recovery of diaphragm muscle from soman poisoning in vitro
AUTHOR(S): Tattersall, John E. H.
CORPORATE SOURCE: Biol. Div., Chem. Biol. Def. Establ., Porton Down/Salisbury/Wiltshire, SP4 0JQ, UK
SOURCE: British Journal of Pharmacology (1993), 108(4), 1006-15
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The actions of oximes and related compds. on the nicotinic acetylcholine receptor ion channel at the adult mouse muscle endplate were investigated by use of single-channel recording techniques. A no. of the compds., including some which lacked the oxime group, produced a significant recovery of neuromuscular function which was unrelated to acetylcholinesterase (AChE) reactivation; this was reversed by washing off the compd., and was therefore attributed to a direct pharmacol. action on the muscle. Some of the compds. blocked open nicotinic receptor ion channels in prepns. of mouse muscle fibers. The compds. which showed the greatest direct pharmacol. actions in diaphragms produce a very fast, flickering blockade of the channels. Several quant. measures of channel-blocking activity correlated very well with the direct pharmacol. action. For 2 compds. studied in greater detail, the direct action and channel-blocking showed similar concn.-response relationships. The results of this study indicate that the direct pharmacol. action of oximes and their analogs against neuromuscular blockade by soman in vitro is due to their channel-blocking activity. The direct action does not correlate well with protection against soman poisoning in vivo.

L30 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:567104 CAPLUS
DOCUMENT NUMBER: 113:167104
TITLE: A new H-oxime restores rat diaphragm contractility after esterase inhibition in vitro
AUTHOR(S): Alberts, Peteris
CORPORATE SOURCE: Div. Exp. Med., Swed. Def. Res. Establ., Umea, S-901 82, Swed.
SOURCE: European Journal of Pharmacology (1990), 184(1), 191-4
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acetylcholine esterase inhibitors block cholinergic neurotransmission. This blockade can be reversed by oximes.

However, a universally effective esterase reactivator does not exist. A new H-oxime, HL.ovrhdot. 7, was tested on rat diaphragm strips. Elec. evoked contractions were blocked by di-2-Pr fluorophosphate, **tabun**, **sarin** and **soman**. Whereas pralidoxime, obidoxime and HI 6 **reversed** the blockade induced by three of these organophosphate compds., LH.ovrhdot. 7 restored the contractions after short blockade induced by all four organophosphate compds. tested.

L30 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1987:133261 CAPLUS
DOCUMENT NUMBER: 106:133261
TITLE: Noncompetitive blockade of the nicotinic acetylcholine receptor-ion channel complex by an irreversible cholinesterase inhibitor
AUTHOR(S): Rao, K. S.; Aracava, Y.; Rickett, D. L.; Albuquerque, E. X.
CORPORATE SOURCE: Sch. Med., Univ. Maryland, Baltimore, MD, 21201, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 240(1), 337-44
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interactions of **VX** [50782-69-9], an irreversible anticholinesterase (anti-ChE) agent, with the nicotinic acetylcholine receptor-ion channel complex (AChR) of the frog Rana pipiens were investigated using electrophysiol. techniques. At low concns. (0.1-0.5 .mu.M) of **VX**, typical effects due to cholinesterase (ChE) inhibition, such as potentiation of indirect muscle twitches as well as increases in the peak amplitude and decay time const. (.tau.EPC) of end-plate currents (EPC), were obsd. At concns. .gtoreq.1.0 .mu.M, **VX** produced opposite effects. The indirectly elicited muscle twitches and PC peak amplitude were depressed with a median inhibitory concn. of .apprx.33 .mu.M. .tau.EPC Was reduced, and at a higher concn. of 100 .mu.M, **VX** split the decays into faster and slower components. Similar results were also obtained with the amplitude and decays of miniature end-plate currents (MEPC). However, although the MEPC peak amplitude and .tau.MEPC were not decreased to levels below control values, EPC peak amplitude (but not its .tau.EPC) was markedly depressed beyond the control values, in a concn.-dependent manner. The fact that nerve action potential-evoked events were more affected than the spontaneous MEPCs suggested an interference with the depolarization-evoked release process. Indeed, **VX** caused a redn. of the quantal content and, in addn., induced an increase in the frequency of MEPCs. All these effects, except the anti-ChE activity, were **reversible** upon wash. The results from both EPC fluctuation anal. and single-channel recordings disclosed a concn.-dependent shortening of the channel-open times without change in single-channel conductance. Most of these effects could be fit to a sequential model and suggest an interaction of **VX** with the open conformation of the nicotinic AChR. At concns. .ltoreq.100 .mu.M, VS did not show any agonist actions on the nicotinic AChR. Aside from the interaction with the junctional AChRs, **VX** seemed not to affect any other properties of the muscle membrane, such as the membrane potential or the time course of action potentials.

L30 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1986:620566 CAPLUS
DOCUMENT NUMBER: 105:220566
TITLE: Organophosphate and carbamate compounds have pre- and postjunctional effects at the insect glutamatergic synapse
AUTHOR(S): Idriss, M. K.; Aguayo, L. G.; Rickett, D. L.; Albuquerque, E. X.
CORPORATE SOURCE: Sch. Med., Univ. Maryland, Baltimore, MD, 21201, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1986), 239(1), 279-85
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the organophosphate compds. diisopropylfluorophosphate (DFP) [55-91-4], **tabun** [77-81-6], **VX** [50782-69-9], and the carbamate physostigmine [57-47-6] were studied on the metathoracic flexor and extensor tibialis muscles of Locusta migratoria. These anticholinesterase (anti-ChE) agents interacted with pre- and postsynaptic regions of the glutamatergic **neuromuscular** synapse. In physiol. soln., contg. normal Ca concn. (2 mM), these agents initiated spontaneous excitatory postsynaptic potentials (EPSPs) and muscle action potentials (APs) alternating with periods of reduced spontaneous activity in which only miniature excitatory postsynaptic potentials (MEPSPs) could be recorded. This spontaneous EPSP and AP firing was influenced by [Ca2+]0; at low concns., the spontaneous APs were abolished but EPSPs and

MEPSPs could still be seen. Further redn. of [Ca2+]0 to 0.2 mM abolished EPSP firing and only MEPSPs were recorded. This spontaneous activity, EPSP and AP, was blocked by tetrodotoxin (0.3 .mu.M). Neither nicotinic nor muscarinic antagonists were able to abolish the presynaptic action of these agents. In addn. to these presynaptic actions, a decrease of the peak amplitude of the excitatory postsynaptic currents (EPSC) was induced by perfusion with DFP, VX, or physostigmine. Only DFP and VX affected the decay time const. of the EPSC. Furthermore, high concns. of tabun did not affect the EPSP. Both the pre- and and postsynaptic effects of these agents were reversible upon washing the prepns. The present results demonstrate a new site of action of these compds. In addn., the lack of effect of physostigmine on the decay phase of EPSCs indicates that the putative receptor-ion channel macromol. for glutamate is able to differentiate various types of anti-ChE agents.

L30 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1984:485264 CAPLUS
DOCUMENT NUMBER: 101:85264
TITLE: Effects of obidoxime chloride on native and sarin-poisoned frog neuromuscular junctions
AUTHOR(S): Caratsch, C. G.; Waser, P. G.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Zurich, Zurich, CH-8006, Switz.
SOURCE: Pfluegers Archiv (1984), 401(1), 84-90
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of obidoxime chloride (I) [114-90-9] on single frog neuromuscular junction was studied to clarify its action on the acetylcholine receptor (AChR) and acetylcholine esterase (AChE) [9000-81-1], both before and after blocking its enzymic activity with sarin [107-44-8]. Expts. with iontophoretic application of I to end-plates demonstrated that I has a weak direct depolarizing effect. Also, I possesses a potentiating effect on the ACh-induced depolarization. After the AChE activity had been inhibited with sarin, I, on the contrary, decreases the depolarization induced by ACh. Both effects are fully reversible. Therefore, I acts as an inhibitor of AChE and as a partial antagonist of the AChR. The antagonistic effect on the receptor is usually masked by the predominating anticholinesterase effect. The effect of I on miniature end-plate potentials in long-time expts. on sarin-poisoned muscles showed only weak signs of recovery from the action of the AChE inhibitor. Only a focally higher concn. of I produced a more marked but short-term recovery of the mepps, which is, however, supposed to be dependent on the AChR antagonism. It is still unclear how much of the varying therapeutic usefulness of I in clin. cases is due to its AChE reactivation and how much to the antagonistic effect on the AChR.

L30 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1973:466943 CAPLUS
DOCUMENT NUMBER: 79:66943
TITLE: Melting temperature of a thermally reversible gel. II. Ethylene-vinyl acetate copolymer-organic solvent gels
AUTHOR(S): Takahashi, Akira
CORPORATE SOURCE: Dep. Appl. Chem., Nagoya Univ., Nagoya, Japan
SOURCE: Polymer Journal (Tokyo, Japan) (1973), 4(4), 379-84
CODEN: POLJB8; ISSN: 0032-3896
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The linear relation between the reciprocal abs. melting temp. of ethylene-vinyl acetate copolymer (I) [24937-78-8] gels in dioxane, EtOAc, MeCOEt, and Me iso-Bu ketone having ethylene mole fractions (xe) 0.64-0.84, and the logarithm of vx (v = I vol. fraction, x = I d.p.) was analyzed using the equation of A. Takahashi et al. (1972); the anal. indicated that the block length of the ethylene unit in the copolymer was 10 regardless of xe. The gels were cryst., and the crystallites (which served as crosslinks) were the ethylene blocks in the copolymer.

L30 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1972:95387 CAPLUS
DOCUMENT NUMBER: 76:95387
TITLE: Synergistic action of 2-(o-cresyl)-4H-1:3:2-benzodioxaphosphorine 2-oxide with soman and physostigmine
AUTHOR(S): McKay, D. H.; Jardine, R. V.; Adie, P. A.
CORPORATE SOURCE: Biomed. Sect., Def. Res. Establ. Suffield, Ralston, AB, Can.
SOURCE: Toxicology and Applied Pharmacology (1971), 20(4),

474-9
CODEN: TXAPA9; ISSN: 0041-008X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In mice, the toxicity of the irreversible cholinesterase inhibitor **soman** (I) [96-64-0] was enhanced >18-fold by prior injection of 2-(o-cresyl)-4H-1,3,2-benzodioxaphosphorine 2-oxide (II) [1222-87-3] (35 mg/kg, s..c.), a metabolite of tri-o-cresyl phosphate [78-30-8]. Under similar conditions, the toxicity of the **reversible** cholinesterase inhibitor physostigmine (III) [57-47-6] was raised <2-fold by II. II apparently **blocks** enzymes degrading I and III, making more of the latter compds. available for cholinesterase inhibition.

L30 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1970:496924 CAPLUS
DOCUMENT NUMBER: 73:96924
TITLE: Protective actions of some anticholinergic drugs in **sarin** poisoning
AUTHOR(S): Brimblecombe, Roger W.; Green, David Morris; Stratton, June A.; Thompson, Pamela B. J.
CORPORATE SOURCE: Min. Def., Chem. Def. Estab., Salisbury, UK
SOURCE: British Journal of Pharmacology (1970), 39(4), 822-30
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The central and peripheral anticholinergic activities of a series of drugs comprising atropine, hyoscine, caramiphen and one of its analogs, and three glycolic acid esters, have been measured. The ability of the same drugs, used alone and in conjunction with N-methylpyridinium-2-aldoxime methanesulfonate (P2S), to protect mice, rats, and guinea pigs from the lethal effects of **sarin** has been assessed. No correlation existed between central or peripheral anticholinergic activity and ability to protect from **sarin**. On the indirectly stimulated isolated rat phrenic nerve-diaphragm prepn., all drugs with the exception of hyoscine caused potentiation of responses to low-frequency stimulation but partial **block** of responses to high-frequency stimulation. The drugs did not **reverse** the effects of **sarin** on the phrenic nerve-diaphragm prepn. A pharmacol. action other than an anticholinergic one is involved, in part, in the protective actions against **sarin** of some of the drugs studied. Whether their effects on skeletal muscle are of any relevance in this respect is unresolved.

L30 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1966:459882 CAPLUS
DOCUMENT NUMBER: 65:59882
ORIGINAL REFERENCE NO.: 65:11193b-c
TITLE: **Reversal** of a **soman**-induced effect on **neuromuscular** function by oximes
AUTHOR(S): Loomis, T. A.
CORPORATE SOURCE: School of Med., Univ. of Washington, Seattle
SOURCE: Life Sciences (1966), 5(14), 1255-61
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An injection of **soman** (I) (60-90 .gamma./kg.) in the anterior tibial muscles of anesthetized atropinized rats caused waves of diminishing amplitude during the initial phase of contraction and a series of bursts, each of which contained multiple waves. 1,1'-Trimethylenebis(4-formylpyridinium chloride) dioxime (II) or 2-pyridine aldoxime methyl trichloroacetate (III) (10-15 mg./kg.) produced a partial to complete **reversal** of the I-induced effect on the action potential and on the twitch response of the muscle within 7 to 10 sec. after their injection. The effect of II on the I-poisoned muscle was not accompanied by reactivation of phosphonylated acetylcholinesterase (IV). The I-induced repetitive depolarization of the anterior tibial muscles can apparently be blocked by the oximes without reactivation of IV; the oximes may produce their effects by an action on the motor nerve terminal resulting in direct blockade of the repetitive discharge.

L30 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1966:108521 CAPLUS
DOCUMENT NUMBER: 64:108521
ORIGINAL REFERENCE NO.: 64:20500c-e
TITLE: **Reversal** of a **soman**-induced effect on **neuromuscular** function without reactivation of cholinesterase
AUTHOR(S): Loomis, Ted A.; Johnson, Dennis D.
CORPORATE SOURCE: School of Med., Univ. of Washington, Seattle
SOURCE: Toxicology and Applied Pharmacology (1966), 8(3),

528-32
CODEN: TXAPA9; ISSN: 0041-008X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The isotonic response of the anterior tibial muscle of the rat to indirectly applied dual stimuli was studied in normal and soman -poisoned animals. Indirectly induced dual responses of the muscle are of equal amplitude in the normal animal at the inter-stimulus intervals employed, but, in the soman-poisoned animal, the response to the 2nd of the dual stimuli is impaired. The amplitude of the 2nd response is directly related to the time interval between the stimuli. Maximal effect on the dual response is evident after a dose of 0.1 mg. of soman /kg. This effect of soman which is accompanied by inhibition of acetylcholinesterase activity in the anterior tibial muscle can be partly or completely reversed, depending on the dose of soman , by administration of piperidylmethylandrostanediol without reactivation of muscle acetylcholinesterase.

L30 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1965:60295 CAPLUS
DOCUMENT NUMBER: 62:60295
ORIGINAL REFERENCE NO.: 62:10738c-d
TITLE: The effect of sodium fluoride on Sarin -inhibited blood cholinesterases
AUTHOR(S): Heilbronn, Edith
CORPORATE SOURCE: Res. Inst. Natl. Defence, Sundyberg, Swed.
SOURCE: Acta Chemica Scandinavica (1964), 18(10), 2410
CODEN: ACHSE7; ISSN: 0904-213X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB During studies on the mechanism of aging of phosphorylated cholinesterases, NaF was tested for its ability to block aging of Sarin inhibited human plasma cholinesterase. Under the conditions used (Veronal buffer) it was found that 10-1M and 10-2M NaF prevented aging; also the compd. itself inhibited plasma cholinesterase at these concns. Repeated expts. with 10-3M and 10-4M NaF showed that the reason for the prevented aging was to be found in a reversal of NaF, meaning that these concns. of NaF were able to restore enzyme activity before any aging of the sample had occurred. Expts. also showed that Sarin inhibited human erythrocyte cholinesterase regains enzyme activity upon addn. of NaF. Enzyme activity of a previously aged Sarin-inhibited plasma cholinesterase prepn. was not restored upon addn. of either 10-3M NaF alone or together with 10-2M N-methylpyridinium-2-aldoxime methanesulfonate.

L30 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1958:7043 CAPLUS
DOCUMENT NUMBER: 52:7043
ORIGINAL REFERENCE NO.: 52:1320d-h
TITLE: Isolated single electroplax preparation. I. Effect of acetylcholine and related compounds
AUTHOR(S): Schoffeniels, Ernest; Nachmansohn, David
CORPORATE SOURCE: Columbia Univ.
SOURCE: Biochimica et Biophysica Acta (1957), 26, 1-15
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A prepn. is described in which an isolated single electroplax of Electrophorus electricus can be used to study the properties of the cell. The electroplax is kept between a nylon sheet having a window adjusted to the dimensions of the cell and a grid consisting of nylon threads. It is placed between 2 chambers in such a way that the cell separates 2 pools of fluid. The innervated membrane of the electroplax is bathed by the fluid of one chamber, the noninnervated one by the fluid of the other. The prepn. permits testing the effect of chem. and phys. factors separately on the innervated and noninnervated faces of the cell and the study of ion flux across the cell. The actions of acetylcholine and of related tertiary and quaternary compds. were investigated. It was confirmed that tertiary N compds. block elec. activity but do not depolarize and are receptor inhibitors; quaternary N derivs. block and depolarize simultaneously and are receptor activators. However, whereas in previous prepns. these effects were irreversible, the following acted reversibly with the new prepn.: acetylcholine, carbamylcholine, eserine, prostigmine, diisopropyl fluophosphate, d-tubocurarine, and procaine. Tabun, decamethonium, and stilbamidine acted irreversibly. The action of nondepolarizing agents was completely reversible, that of depolarizing compds. could be only partially reversed, and then only temporarily. The compds. acted whether applied to the soln. bathing the innervated or noninnervated membrane. Depolarization of the cell by the quaternary derivs. was the result of

action on the synaptic region. Blocking and depolarization by quaternary derivs. could not be dissocd.; expts. with curare showed that they acted only upon the synaptic junction. Both tertiary and quaternary compds. tested competed for the same receptor.

L30 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1955:70786 CAPLUS
DOCUMENT NUMBER: 49:70786
ORIGINAL REFERENCE NO.: 49:13506i,13507a-b
TITLE: Effect of certain tri-substituted phosphine oxides on synaptic conduction in the roach, Periplaneta americana
AUTHOR(S): Roeder, Kenneth D.; Kennedy, Nancy K.
CORPORATE SOURCE: Tufts Univ., Medford, MA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1955), 114, 211-20
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The effects of **Tabun**, **Sarin**, **Soman**, and 4 other methyl-alkoxy-fluorophosphine oxides were studied on synaptic conduction in the last abdominal ganglion of the roach. The most active compd. was methyl(1-methyl-2,2-dimethylpropoxy)fluorophosphine oxide. When applied directly to the ganglion, it caused synaptic instability and after-discharge in 5.7 .times. 10-11M soln. The effect was irreversible and was probably due to inactivation of cholinesterase. Higher concns. sometimes caused a normal-appearing synchronized synaptic response and eventual synaptic **block**; these effects could be removed by washing with saline soln. Atropine, d-tubocurarine, scopolamine, and acetylcholine had little or no effect on these changes produced by all of the phosphine derivs. The phosphine derivs. abolished the stimulating effect of nicotine on the roach nerve cord. The **reversible** effects of the compds. could be due to competition with the mediator for the receptor.

L36 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:710454 CAPLUS
TITLE: Reversal of Neuromuscular Blockade and Simultaneous Increase in Plasma Rocuronium Concentration after the Intravenous Infusion of the Novel Reversal Agent Org 25969
AUTHOR(S): Epemolu, Ola; Bom, Anton; Hope, Frank; Mason, Rona
CORPORATE SOURCE: Department of Pharmacology, Organon Research, UK
SOURCE: Anesthesiology (2003), 99(3), 632-637
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BACKGROUND: The purpose of this study was to det. the changes in the plasma concn. of rocuronium and the reversal of its neuromuscular blockade after the i.v. infusion of Org 25969, the novel neuromuscular block-reversal agent, in anesthetized guinea pigs. METHODS: Rocuronium was infused for 1 h at a rate of 12-19 nmol.cntdot.kg-1.cntdot.min-1 to produce a steady-state 90% neuromuscular block. After 30 min, a concomitant infusion of either the reversal agent Org 25969 at a rate of 50 nmol.cntdot.kg-1.cntdot.min-1 or an infusion of an equiv. vol. of saline was started. The time course of plasma concns. of rocuronium was detd. by use of liq. chromatog.-mass spectrometry/mass spectrometry. RESULTS: In both treatment groups, a steady-state plasma concn. of rocuronium was obtained after 30 min. In the saline-treated group, the plasma concn. of rocuronium and depth of block remained const. In the Org 25969 group, neuromuscular block was reversed while the rocuronium infusion was ongoing. Simultaneously, an increase in the total plasma concn. of rocuronium (free and complexed) was obsd., even though the infusion rate of rocuronium was not changed. Compared with the saline-treated group, a small increase in the postmortem bladder concn. of rocuronium was detected. CONCLUSIONS: The authors propose that the capture of rocuronium by Org 25969 causes the rapid reversal of neuromuscular block. The reversal can be explained by the rapid transfer of free rocuronium from the effect compartment (neuromuscular junction) to the central compartment, in which it is bound to Org 25969. This explains the increase in total plasma concn. of rocuronium (free and bound to Org 25969).
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:607157 CAPLUS
TITLE: Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal ?
AUTHOR(S): Zhang, Ming-Qiang
CORPORATE SOURCE: Organon Laboratories Ltd., Lanarkshire, ML1 5SH, UK
SOURCE: Drugs of the Future (2003), 28(4), 347-354
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chem. modification of .gamma.-cyclodextrin afforded Org-25969 that has a cavity dimension capable of forming a binary host-guest complex with the steroidal neuromuscular blocker rocuronium bromide with high affinity. In this complex, rocuronium is encapsulated inside the cavity of Org-25969. As a consequence, the neuromuscular blocking activity of rocuronium can be reversed by Org-25969. The reversal produced by Org-25969 is more efficacious than the std. combination of acetylcholinesterase inhibitor and muscarinic receptor antagonist, e.g., neostigmine + atropine. Unlike neostigmine + atropine, Org-25969 does not interfere with the acetylcholine homeostasis. At the effective reversal dose (0.5 .mu.mol/kg i.v.), Org25969 produced negligible changes in hemodynamic parameters in anesthetized guinea pigs, cats and monkeys. Org-25969 is also effective in reversing profound block induced by 3 times the ED90 of rocuronium in guinea pigs at a rate at least 3 times faster than neostigmine + atropine. Therefore, Org-25969 is also potentially useful for early or escape reversal of rocuronium, for instance, in a "cannot intubate, cannot ventilate" situation.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:51184 CAPLUS
DOCUMENT NUMBER: 138:83270
TITLE: Residual paralysis induced by either **vecuronium** or **rocuronium** after **reversal** with pyridostigmine
AUTHOR(S): Kim, Kyo S.; Lew, Se H.; Cho, Hee Y.; Cheong, Mi A.
CORPORATE SOURCE: Department of Anesthesiology, Hanyang University Hospital, Seoul, S. Korea
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (2002), 95(6), 1656-1660
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated postoperative residual curarization after administration of either **vecuronium** or **rocuronium** with **reversal** by pyridostigmine in 602 consecutive patients without perioperative **neuromuscular** monitoring. On arrival in the recovery room, **neuromuscular** function was assessed both by acceleromyog. in a train-of-four (TOF) pattern and also clin. by the ability to sustain a head-lift for >5 s and the tongue-depressor test. Postoperative residual curarization was defined as a TOF ratio <0.7. One fifth of 602 patients (**vecuronium**, 24.7%; **rocuronium**, 14.7%) had a TOF <0.7 in the recovery room. There were no significant differences in the TOF ratios between 10 mg and 20 mg of pyridostigmine. The patients with residual **block** had several assocd. factors: the absence of perioperative **neuromuscular** monitoring, the use of pyridostigmine, which is less potent than neostigmine, a larger dose of **vecuronium**, shorter time from the last **neuromuscular** blocker to TOF monitoring, or peripheral cooling. We conclude that significant residual **neuromuscular block** after **vecuronium** or **rocuronium** was not eliminated even with **reversal** by a large dose of pyridostigmine.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:641079 CAPLUS
DOCUMENT NUMBER: 138:106579
TITLE: Quaternary Salts of E2020 Analogues as Acetylcholinesterase Inhibitors for the **Reversal** of **Neuromuscular Block**
AUTHOR(S): Clark, John K.; Cowley, Phill; Muir, Alan W.; Palin, Ronald; Pow, Eleanor; Prosser, Alan B.; Taylor, Robert; Zhang, Ming-Qiang
CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd., Lanarkshire, ML1 5SH, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(18), 2565-2568
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:106579
AB A series benzylpiperidinium and benzylpyridinium quaternary salts was synthesized and tested for inhibition of acetylcholinesterase and **reversal** of **neuromuscular block** induced by **vecuronium**. Several potent **reversal** agents were identified and their haemodynamic effects measured.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:251270 CAPLUS
DOCUMENT NUMBER: 137:226182
TITLE: 2-O-Substituted Cyclodextrins as Reversal Agents for the **Neuromuscular** Blocker **Rocuronium** Bromide
AUTHOR(S): Tarver, Gary J.; Grove, Simon J. A.; Buchanan, Kirsteen; Bom, Anton; Cooke, Andrew; Rutherford, Samantha J.; Zhang, Ming-Qiang
CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire, ML1 5SH, UK
SOURCE: Bioorganic & Medicinal Chemistry (2002), 10(6), 1819-1827
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of secondary face modified cyclodextrins (CDs) were synthesized with the aim of constructing host mols. capable of forming host-guest complexes with **neuromuscular** blockers, esp. with **rocuronium** bromide. Perfacial 2-O-substitution of .gamma.-CD with 4-carboxybenzyl resulted in a CD host mol. 1 that forms a 1:1 binary complex with **rocuronium** bromide (Ka 6.2.times.105 M-1). The biol. activities of this compd. and other derivs. as **reversal** agents of **rocuronium** bromide were examd. in vitro (mouse hemi-diaphragm) and in vivo (anesthetized guinea pigs). The host mol. 1 was found to exert potent **reversal** activity (ED50 0.21 .mu.mol/kg, iv) against **rocuronium**-induced **neuromuscular block**, and thus proved the viability of using host mols. as antidotes of a biol. active compd.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:136911 CAPLUS

DOCUMENT NUMBER: 137:103386

TITLE: Anionic Cyclophanes as Potential **Reversal** Agents of Muscle Relaxants by Chemical Chelation

AUTHOR(S): Cameron, Kenneth S.; Fielding, Lee; Mason, Rona; Muir, Alan W.; Rees, David C.; Thorn, Simon; Zhang, Ming-Qiang

CORPORATE SOURCE: Department of Analytical Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire, ML1 5SH, UK

SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(5), 753-755
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:103386

AB A series of carboxyl-contg. cyclophanes have been designed and synthesized as chem. chelators (or host mols.) of cationic muscle relaxant drugs (or guest mols.). These cyclophane derivs. have been shown by NMR to form 1:1 complexes with the muscle relaxants **pancuronium**, and gallamine, in D2O, with assocn. consts. up to 104 M-1. When tested in an in vitro chick biventer muscle prepn., the cyclophanes **reversed** the **neuromuscular block** induced by **pancuronium** and gallamine, with I having the most effective **reversal** against **pancuronium** (EC50 40 .mu.M).

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:1476 CAPLUS

DOCUMENT NUMBER: 136:385923

TITLE: Oxyaniliniums as acetylcholinesterase inhibitors for the **reversal** of **neuromuscular block**

AUTHOR(S): Grove, Simon J. A.; Kaur, Jasmit; Muir, Alan W.; Pow, Eleanor; Tarver, Gary J.; Zhang, Ming-Qiang

CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire, NL1 5SH, UK

SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(2), 193-196
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of oxyanilinium-based AChE inhibitors have been synthesized and tested for the **reversal** of **vecuronium**-induced **neuromuscular block**. Several compds., for example 2-hydroxy- and 2-methoxy-N,N-dimethyl-N-allylanilinium bromide showed comparable **reversal** potencies to edrophonium and clean in vivo cardiovascular profiles. Compds. thus tested included 2-hydroxy-N,N-dimethyl-N-2-propenylbenzenaminium bromide, 3-hydroxy-N,N-dimethyl-N-2-propenylbenzenaminium bromide, 4-hydroxy-N,N-dimethyl-N-2-propenylbenzenaminium bromide, 3-hydroxy-N,N-dimethyl-N-2-propenylbenzenemethanaminium bromide, 3-methoxy-N,N-dimethyl-N-2-propenylbenzenemethanaminium bromide, etc.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:640126 CAPLUS

TITLE: Chemical chelation as a novel method of NMB **reversal**: Discovery of a synthetic

cyclodextrin Org 25969
AUTHOR(S): Zhang, Ming-Qiang; Bom, Anton; Cameron, Kenneth S.; Clark, John K.; Feilden, Helen; Hutchinson, Edward; Muir, Alan W.; Palin, Ronald; Rees, David C.
CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd, Lanarkshire, N/A, UK
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-307. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB We hypothesized that chem. chelation of neuromuscular blockers (NMBAs) by an exogenous host mol. such as cyclodextrins would promote the dissocn. of NMBAs from their site of action, i.e., nAChR on the muscle, leading to the reversal of neuromuscular blockade. Since this mechanism of action does not involve direct activation of cholinergic systems, it may circumvent the undesired side-effects attendant with AChE inhibitors such as neostigmine. It has also the potential advantage to be used for the reversal of both depolarizing and non-depolarizing NMBAs, because of this lack of involvement of nAChRs in the mechanism of action. In addn., the chelators may further be safely employed for the reversal of -profound (or complete) block'. In this presentation we shall describe the discovery of Org 25969, a synthetic cyclodextrin-based host mol. that forms tight host-guest complex with rocuronium and as a result reverses rocuronium-induced neuromuscular block. The reversal produced by Org 25969 is not only fast and highly efficient, but also without any visible CV side-effects. The designed synthesis of this NCE as well as its complexation thermodn. with rocuronium will be discussed.

L36 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:417024 CAPLUS
DOCUMENT NUMBER: 135:29151
TITLE: 6-mercaptocyclodextrin derivatives, their preparation, and the use as reversal agents for drug-induced neuromuscular block
INVENTOR(S): Zhang, Mingqiang; Palin, Ronald; Bennet, David Jonathan
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001040316	A1	20010607	WO 2000-EP11789	20001123
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000015947	A	20020820	BR 2000-15947	20001123
EP 1259550	A1	20021127	EP 2000-993261	20001123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NZ 518752	A	20030328	NZ 2000-518752	20001123
JP 2003515623	T2	20030507	JP 2001-541070	20001123
NO 2002002522	A	20020528	NO 2002-2522	20020528

PRIORITY APPLN. INFO.: EP 1999-309558 A 19991129
WO 2000-EP11789 W 20001123
OTHER SOURCE(S): MARPAT 135:29151
AB 6-Mercaptocyclodextrin derivs. I [m = 0-7; n = 1-8; m + n = 7 or 8; R = C1-6 alkylene (optionally substituted with 1-3 OH), (CH2)o-phenylene-(CH2)p (o, p = 0-4); X = COOH, CONHR1, NHCOR2, SO2OH, PO(OH)2, O(CH2CH2O)qH, OH, tetrazol-5-yl; R1 = H, C1-3 alkyl; R2 = carboxyphenyl; q = 1-3], or pharmaceutically acceptable salts thereof, are disclosed. The 6-mercaptocyclodextrin derivs. is highly suitable for use in the reversal of drug-induced neuromuscular block.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:137035 CAPLUS
DOCUMENT NUMBER: 134:193457
TITLE: Use of chemical chelators as reversal agents for drug-induced neuromuscular block
INVENTOR(S): Bom, Antonius Helena Adolf; Muir, Alan William; Rees, David
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012202	A2	20010222	WO 2000-EP7694	20000807
WO 2001012202	A3	20011115		
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013126	A	20020423	BR 2000-13126	20000807
EP 1210090	A2	20020605	EP 2000-964006	20000807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507335	T2	20030225	JP 2001-516547	20000807

PRIORITY APPLN. INFO.: EP 1999-306411 A 19990813
WO 2000-EP7694 W 20000807

OTHER SOURCE(S): MARPAT 134:193457

AB Cyclophanes I [R = (CH2)5, 4-CH2C6H4CH2, 1,4-cyclohexanediyldimethylene; n = 1, 2, 3] and II [X = (CH2)5, 4-CH2C6H4CH2, 2,6-naphthalenediyldimethylene] were prepd. Thus, the tetra-Me ester of I [R = (CH2)5, n = 2] was prepd. from 1,7,21,27-tetraaza[7.1.7.1]paracyclophane and 3-(methoxycarbonyl)propionyl chloride and was sapond. to give the tetracarboxylic acid. Both in vivo tests of cyclodextrin derivs. and in vitro tests of I, II, and cyclodextrin derivs. as **reversal** agents for drug-induced **neuromuscular block** were described.

L36 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:191478 CAPLUS
DOCUMENT NUMBER: 132:203084
TITLE: **Reversal** of **rapacuronium** **block** during propofol versus sevoflurane anesthesia
AUTHOR(S): Zhou, Tian J.; Tang, Jun; White, Paul F.; Joshi, Girish P.; Wender, Ronald; Murphy, Mark T.; Chiu, Jen W.; Webb, Tom
CORPORATE SOURCE: Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, 75235-9068, USA
SOURCE: Anesthesia & Analgesia (Baltimore) (2000), 90(3), 689-693
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the antagonism of **rapacuronium** with edrophonium-atropine during propofol- or sevoflurane-based anesthesia in 60 healthy outpatients. After the induction of anesthesia with standardized doses of propofol and fentanyl, **rapacuronium** 1.5 mg/kg was administered to facilitate tracheal intubation. Patients were randomized to receive either a propofol infusion (100 .mu.g .bul. kg-1 .bul. min-1) or sevoflurane (1.0%, end-tidal) in combination with nitrous oxide 66% for maintenance of anesthesia. **Neuromuscular** **block** was monitored by using electromyog. at the wrist and **reversed** with edrophonium 1.0 mg/kg and atropine 0.015 mg/kg when the first twitch (T1) response of the train-of-four (TOF) stimulation recovered to 25% of the baseline value. The clin. duration of action (i.e., time to 25% T1 recovery) was similar during both propofol (13.1.+-.3.6 min) and sevoflurane (13.7.+-.4.4 min) anesthesia. The time from 25% T1 recovery to TOF ratio of 0.8 was also similar with propofol (3.4.+-.2.1 min) and sevoflurane (5.9.+-.8.7 min) (P > 0.05). Although none of the patients in the propofol group required more than 9 min to achieve a TOF ratio of 0.8, two patients receiving sevoflurane required 31 min and 37 min. Adequate antagonism of **rapacuronium**

block with edrophonium can be achieved within 10 min during propofol anesthesia. However, more prolonged recovery may occur in the presence of sevoflurane. Implications: We studied the reversal of rapacuronium-induced block with edrophonium and found that the residual rapacuronium block can be readily antagonized during propofol-based anesthesia. However, reversal of rapacuronium appears to be less predictable during sevoflurane-based anesthesia.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:458682 CAPLUS
DOCUMENT NUMBER: 131:125280
TITLE: Early reversal of rapacuronium with neostigmine
AUTHOR(S): Purdy, Robert; Bevan, David R.; Donati, Francois; Lichtor, J. Lance
CORPORATE SOURCE: Department of Anaesthesia, University of British Columbia, Vancouver, BC, V5Z 4E3, Can.
SOURCE: Anesthesiology (1999), 91(1), 51-57
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This multiple-center study detd. recovery from neuromuscular blockade when neostigmine was given 2 or 5 min after rapacuronium . Patients were randomized to receive 2 different doses of rapacuronium and to receive neostigmine in 2 different doses and at 2 different times. During propofol anesthesia with N2O, O, and fentanyl, 1.5 or 2.5 mg rapacuronium/kg was given 1 min before tracheal intubation. Neuromuscular block was measured by train-of-four ulnar nerve stimulation every 12 s: the adductor pollicis force of contraction was recorded mechanomyog. Two or five minutes after rapacuronium was administered, 0.05 or 0.07 mg neostigmine/kg was administered and recovery was compared with that of control patients who received no neostigmine. Both doses of rapacuronium produced 100% block in all but one patient, who exhibited 97% block. Neostigmine accelerated recovery in all groups. Overall, recovery of intense rapacuronium block was accelerated by early neostigmine administration. When given 2 min after rapacuronium, neostigmine was as effective as when given after 5 min, and 0.05 mg neostigmine/kg was comparable to 0.07 mg/kg.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:397693 CAPLUS
DOCUMENT NUMBER: 131:67546
TITLE: Monitoring and reversal of neuromuscular block
AUTHOR(S): Bevan, David R.
CORPORATE SOURCE: Department of Anesthesia, University of British Columbia, Vancouver, BC, Can.
SOURCE: American Journal of Health-System Pharmacy (1999), 56(Suppl. 1), S10-S13
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 24 refs. Methods of monitoring and reversing neuromuscular blocking agents to avoid residual neuromuscular block are described. Studies have shown that if a long-acting neuromuscular blocking agent is used during anesthesia, the frequency of residual block, regardless of the method of neuromuscular monitoring, will be at least 20%. In the past 20-25 yr, anesthesiologists have come to use some form of nerve stimulation to monitor the degree of residual neuromuscular block; there are various patterns of stimulation, including train-of-four (TOF) stimulation and double-burst stimulation (DBS). For both TOF stimulation and DBS, the response to the stimuli in a series fades such that the last response can be expressed as a ratio of the first. The fade to DBS is the same as that to TOF stimulation. Clinicians can clin. detect a fade in TOF response when the TOF ratio is <0.5. Fade to DBS is easier to detect than that to TOF stimulation, but, as the block recovers, the anesthesiologist's ability to detect fade decreases. Although anesthesiologists have accepted a TOF ratio of at least 0.7 as the std., studies of vecuronium neuromuscular block have shown an impaired ventilatory response to hypoxemia and the possibility of increased risk of aspiration

* state of art

until the TOF ratio recovered to 0.9. The use of **pancuronium** and a persistent TOF ratio of 0.7 in the postanesthesia care unit was shown to be assocd. with a threefold greater occurrence of postoperative pulmonary complications compared with **vecuronium** of atracurium. Spontaneous recovery from **neuromuscular block** occurs through redistribution, metab., or buffered diffusion, but recovery can be accelerated by administration of anticholinesterase agents, such as neostigmine and edrophonium. Studies suggest that even intermediate-duration agents should be **reversed**. **Rapacuronium** is a new investigational drug with similar onset characteristics to succinylcholine and, if **reversed** early, similar recovery characteristics. Postoperative residual **neuromuscular block** is frequent, dangerous, and difficult to recognize clin. The action of **neuromuscular** blocking agents should always be **reversed** unless there is unequivocal evidence of adequate function.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:530206 CAPLUS
DOCUMENT NUMBER: 127:199933
TITLE: **Reversal** of **vecuronium** and **pipecuronium neuromuscular block** by neostigmine in dogs
AUTHOR(S): Madhavi, D.; Sreenu, Makkena; Ramakrishan, O.
CORPORATE SOURCE: Acharya N G Ranga Agricultural University, Tirupati, 517 502, India
SOURCE: Indian Journal of Animal Sciences (1997), 67(6), 509-510
CODEN: IJLAA4; ISSN: 0367-8318
PUBLISHER: Indian Council of Agricultural Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two non-depolarizing muscle relaxants, **vecuronium** bromide and **pipecuronium** bromide, were compared with regard to their **neuromuscular block** and **reversal** with neostigmine in dogs. **Vecuronium** bromide (0.08 mg/kg) and **pipecuronium** bromide (0.04 mg/kg) produced good muscle relaxation in 10 and 40 min, resp., which was completely **reversed** by neostigmine. The **reversal** was quicker in **vecuronium** group compared to that in **pipecuronium** group; this might be due to the vagolytic and sympathetic stimulation of the **pipecuronium** , whereas **vecuronium** does not show these effects. It is concluded that neostigmine can be safely used to **reverse** the effects of the two non-depolarizing relaxants.

L36 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:412713 CAPLUS
DOCUMENT NUMBER: 127:75937
TITLE: Factors affecting neostigmine **reversal** of **vecuronium block** during sevoflurane anesthesia
AUTHOR(S): Morita, T.; Kurosaki, D.; Tsukagoshi, H.; Shimada, H.; Sato, H.; Goto, F.
CORPORATE SOURCE: Department of Anesthesiology and Reanimatology, Gunma University School of Medicine, Maebashi, 371, Japan
SOURCE: Anaesthesia (1997), 52(6), 538-543
CODEN: ANASAB; ISSN: 0003-2409
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We examd. the influence of the concn. of sevoflurane and the degree of muscle **block** at the time of **reversal** on the activity of neostigmine. Ninety ASA 1-2 patients were anesthetized with 0.2, 0.7 or 1.2 MAC of sevoflurane (30 patients each) in 66% nitrous oxide in oxygen. The electromyog. (EMG) response of the adductor digiti minimi was monitored at 20-s intervals after train-of-four stimulation of the ulnar nerve. The initial **neuromuscular block** was produced by **vecuronium** 100 .mu.g.kg-1. When the amplitude of the first response (T1) values had recovered to 10%, 25% or 40% of the control, neostigmine 40 .mu.g.kg-1 was administered. The train-of-four ratio values were recorded at 1-min intervals during the subsequent 15-min period. Higher end-tidal concns. ($p < 0.0001$) and more pronounced **block** at the time of **reversal** ($p < 0.0001$) were assocd. with a delayed recovery in the train-of-four ratio. In addn., the train-of-four ratio 15 min after neostigmine administration was more dependent on the sevoflurane concn. than on the degree of **block** present ($p < 0.0001$). These results confirm that neostigmine (40 .mu.g.kg-1) can **reverse** **vecuronium**-induced but not

sevoflurane-induced neuromuscular block.

L36 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:426735 CAPLUS
DOCUMENT NUMBER: 125:104946
TITLE: Conditions to optimize the reversal action of neostigmine upon a vecuronium-induced neuromuscular block
AUTHOR(S): Baurain, M. J.; Dernovoi, B. S.; D'Hollander, A. A.; Hennart, D. A.; Cantraine, F. R.
CORPORATE SOURCE: Department Anesthesiology, University Hospital Erasme, Brussels, Belg.
SOURCE: Acta Anaesthesiologica Scandinavica (1996), 40(5), 574-578
CODEN: AANEAB; ISSN: 0001-5172
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Since neostigmine was introduced for reversal of neuromuscular block, there has been controversy about the optimum dose for antagonizing neuromuscular block. The purpose of this study was to characterize recovery of neuromuscular transmission following a vecuronium -induced block 15 min after neostigmine administration using different stimulation patterns, and to det. the effects of different doses of neostigmine given at various pre-reversal twitch heights. Adductor pollicis (AP) mech. activity in response to low (0.1 and 2 Hz) and high (50 and 100 Hz) frequency stimulation, was recorded 15 min after 20, 40 and 80 .mu.g/kg neostigmine, given to reverse a vecuronium-induced block at 10, 25 and 50% pre-reversal twitch height (TH). Fifty four ASA class I and II anesthetized (methohexital, fentanyl, N2O/O2) young adult patients were studied and randomly allocated into 9 groups of 6 patients each. In contrast to twitch height (TH) and residual force after 50 Hz, 5 s tetanic stimulation (RF50Hz), the greater sensitivity of train-of-four (TOF) ratio and residual force after 100 Hz, 5 s tetanic stimulation (RF100Hz) points out the best reversal conditions (prereversal TH and the optimal neostigmine dose) (two-way anal. of variance). The highest reversal scores (about 0.9 TOF ratio and RF100Hz) were obtained when 40 .mu.g/kg of neostigmine was given at 25 and 50% TH. A 0.9 TOF ratio was also obsd. when 40 .mu.g/kg of neostigmine was given at 10% TH, but, under these conditions, RF100Hz was only 0.6 (Duncan test). To optimize the reversal action of neostigmine to obtain the highest neuromuscular transmission recovery (0.9 TOF ratio and RF100Hz) during a vecuronium-induced neuromuscular block, the 40 .mu.g/kg dose has to be given at 25 to 50% recovery of TH.

L36 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:115780 CAPLUS
DOCUMENT NUMBER: 124:220264
TITLE: Neostigmine reversal of vecuronium neuromuscular block and the influence of renal failure
AUTHOR(S): Dhonneur, Gilles; Rebaine, Chawky; Slavov, Velislav; Ruggier, Romanie; De Chaubry, Veronique; Duvaldestin, Philippe
CORPORATE SOURCE: Henri Mondor Hospital, University Paris, Creteil, F-94010, Fr.
SOURCE: Anesthesia & Analgesia (Baltimore) (1996), 82(1), 134-8
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The duration of clin. relaxation induced by vecuronium and reversal by neostigmine was studied in 40 patients with renal failure (RF) and 40 patients with normal renal function (NL) under general anesthesia. Patients were premedicated with flunitrazepam, and anesthesia commenced with fentanyl 1-2 .mu.g/kg, thiopental 5-8 mg/kg, and vecuronium 0.1 mg/kg. Anesthesia was maintained with 60% nitrous oxide in oxygen, isoflurane 0.3%-1.0% end-tidal concn., and 1 .mu.g/kg fentanyl every 20-30 min. Neuromuscular block was reversed by the administration of i.v. neostigmine 40 mg/kg at the time of reappearance of either two or four responses to the train-of-four (TOF) stimulation. Monitoring of neuromuscular function consisted of supramaximal TOF stimulation of the ulnar nerve and the evoked thumb response was registered using a force transducer. Spontaneous recovery time, reversal time, and the time to recovery of TOF ratio to 0.7 were recorded. RF did not prolong the

vecuronium neuromuscular blocking effect, reversal was achieved at the same rate in NL as in RF, and the duration of reversal of neuromuscular blocking effect, of vecuronium was not influenced by the time of administration of neostigmine. Therefore, the neuromuscular blocking effect of a tracheal intubating dose of vecuronium can be reversed at the same rate in patients with end-stage RF as in patients with normal kidney function.

L36 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:205127 CAPLUS
DOCUMENT NUMBER: 118:205127
TITLE: Reversal by suramin of neuromuscular block produced by pancuronium in the anesthetized rat
AUTHOR(S): Henning, Robert H.; Nelemans, Adriaan; Houwertjes, Martin; Agoston, Sandor
CORPORATE SOURCE: Dep. Pharmacol./Clin. Pharmacol., Univ. Groningen, Groningen, 9713 BZ, Neth.
SOURCE: British Journal of Pharmacology (1993), 108(3), 717-20
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rats were anesthetized with sodium pentobarbitone and maximal twitches of the tibialis anterior muscle were evoked by elec. stimulation of the motor nerve. Suramin, injected i.v. in a series of cumulative bolus doses at 15 mg/kg each, completely reversed the 90% depression of twitches maintained by a continuous i.v. infusion of pancuronium. The cumulative dose necessary to restore the twitches to 50% of their control amplitude was 35 mg/kg. Suramin did not modify the block produced by suxamethonium, nor did it affect the amplitude of control maximal twitches even in cumulative doses up to 150 mg/kg. The effects of bolus doses of suramin (85 mg/kg), neostigmine (0.03 mg/kg), and 4-aminopyridine (1.2 mg/kg), calcd. to restore pancuronium -blocked twitches to 95% of control amplitude, were compared. Suramin produced the most rapid reversal (1.1 min), but its duration of action was the shortest (9.4 min). Suramin was without effect on the heart rate or blood pressure in the doses used. Thus, suramin reversed the neuromuscular block produced by the nondepolarizing blocking drug pancuronium, but was without effect on the block produced by the depolarizing neuromuscular blocker suxamethonium. Its short duration of action suggests that suramin would probably not be of clin. value as a reversal agent. It might serve as a starter compd. for the development of new reversal agents for anesthetic practice.

L36 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1992:563690 CAPLUS
DOCUMENT NUMBER: 117:163690
TITLE: Modification of atracurium or vecuronium blockade and their reversal by succinylcholine in the cat
AUTHOR(S): Shin, Yang Sik; Yoo, Eun Sook; Min, Sang Kee; Kim, Jong Rae; Park, Kwang Won
CORPORATE SOURCE: Coll. Med., Yonsei Univ., Seoul, 120-752, S. Korea
SOURCE: Yonsei Medical Journal (1992), 33(1), 81-6
CODEN: YOMJA9; ISSN: 0513-5796
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interaction between succinylcholine (SCC) and non-depolarizers, atracurium or vecuronium was investigated in 36 cats of either sex using the sciatic nerve-anterior tibialis muscle prepn. Addnl., the relation of SCC to pseudocholinesterase activity was examd. The duration of action of vecuronium (6.5 to 7.3 min) in cats pretreated with SCC was greater than those (2.0 min) in non-pretreated cats. However, SCC had no influence on the duration of atracurium. The serum pseudocholinesterase activity was decreased after the injection of atracurium or neostigmine in contrast to vecuronium. The authors conclude that the prior administration of SCC prolongs the duration of vecuronium but not that of atracurium, and pseudocholinesterase activity is not related to the prolonging effect of SCC.

L36 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1988:16155 CAPLUS
DOCUMENT NUMBER: 108:16155
TITLE: Neuromuscular block produced by vecuronium-verapamil and reversal of combined blockade with edrophonium at the rat neuromuscular junction

AUTHOR(S): Suer, A. H.; Wali, F. A.; McAteer, E.; Withington, P. S.; Dark, C. H.; Bradshaw, E. G.
CORPORATE SOURCE: Med. Coll., London Hosp., Whitechapel/London, UK
SOURCE: Acta Anaesthesiologica Italica (1986), 37(6), 867-75
CODEN: AANIBO; ISSN: 0374-4965
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of verapamil on **vecuronium**-induced **neuromuscular** blockade, and **reversal** of the combined verapamil-**vecuronium** blockade with edrophonium was studied in vitro, at the rat **neuromuscular** junction. Furthermore, the effect of **vecuronium** on the indirectly-elicited tetanic contractions, evoked at 1-100 Hz, was studied to see if **vecuronium** modified the presynaptic release of transmitter, acetylcholine (ACh) at the rat **neuromuscular** junction. The results showed that (a) **vecuronium** is a potent short acting muscle relaxant at the rat skeletal muscle, (b) verapamil, in low concn., which has no **neuromuscular** effect on its own, markedly potentiated **vecuronium**-induced blockade, (c) edrophonium effectively **reversed** the **vecuronium** and **vecuronium** -verapamil blockade, and (d) **vecuronium** significantly reduced the tetanic contractions, evoked at 1-100 Hz of phrenic nerve stimulation, suggesting a possible prejunctional inhibitory effect of **vecuronium** at the rat **neuromuscular** junction. These and other results concerning **vecuronium**-verapamil and **reversal** with anticholinesterase agents are discussed in terms of pre- and post-junctional effects of drugs at the **neuromuscular** junction.

L36 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1985:534928 CAPLUS
DOCUMENT NUMBER: 103:134928
TITLE: **Neuromuscular** blocking action of **vecuronium** in the dog and its **reversal** by neostigmine
AUTHOR(S): Jones, R. S.
CORPORATE SOURCE: Univ. Dep. Anaesth., R. Liverpool Hosp., Liverpool, L69 3BX, UK
SOURCE: Research in Veterinary Science (1985), 38(2), 193-6
CODEN: RVTSA9; ISSN: 0034-5288
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Vecuronium** bromide (I) [50700-72-6] is one of a new series of competitive or nondepolarizing muscle relaxants which is closely related chem. to **pancuronium**. Doses of 0.06, 0.1 and 0.2 mg/kg produced **neuromuscular block** in the anesthetized dog. There were no observable effects on arterial blood pressure. The **neuromuscular block** was rapidly **reversible** with neostigmine [59-99-4] preceded by atropine.

L36 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1982:520420 CAPLUS
DOCUMENT NUMBER: 97:120420
TITLE: Observations on the **neuromuscular** blocking action of gallamine and **pancuronium** and their **reversal** by neostigmine
AUTHOR(S): Gleed, R. D.; Jones, R. S.
CORPORATE SOURCE: Dep. Anaesthesia, R. Liverpool Hosp., Liverpool, UK
SOURCE: Research in Veterinary Science (1982), 32(3), 324-6
CODEN: RVTSA9; ISSN: 0034-5288
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **neuromuscular** blocking action of gallamine triethiodide (I) [65-29-2] and **pancuronium** bromide (II) [15500-66-0] was investigated in the dog using train-of-four stimuli. The mean duration of gallamine was 29 min and that of **pancuronium** was 31 min. **Reversal** of the **neuromuscular block** was produced by atropine [51-55-8] and neostigmine [59-99-4].

L36 ANSWER 23 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1978:99237 CAPLUS
DOCUMENT NUMBER: 88:99237
TITLE: Clinical pharmacology of the **reversal** of **neuromuscular block**
AUTHOR(S): Gyermek, L.
CORPORATE SOURCE: Sch. Med., Univ. California, Davis, CA, USA
SOURCE: International Journal of Clinical Pharmacology and Biopharmacy (1977), 15(8), 356-62
CODEN: IJCBDX; ISSN: 0340-0026
DOCUMENT TYPE: Journal

LANGUAGE: English

AB In anesthetized surgical patients, the restoration of skeletal muscle function by anticholinesterase agents and atropine analogs following **pancuronium** bromide [15500-66-0] **block** were studied. Effects on the cardiovascular system and on the secretory system were detd. Pyridostigmine advantageously replaced neostigmine in the **reversing** regimen. Replacement of atropine with either one of the following 3 synthetic quaternary ammonium type of parasympathetic blocking drugs, glycopyrrolate, propantheline bromide, and scopolamine bromide, potentially eliminated central nervous system toxicity. Furthermore, glycopyrrolate and propantheline bromide in combination with pyridostigmine produced less abrupt changes in the heart rate than the atropine-neostigmine mixt. [64239-08-3] or the atropine-pyridostigmine bromide mixt. [64239-09-4]. The moderately long onset of action of pyridostigmine was accelerated by the addn. of edrophonium, a rapidly acting anticholinesterase agent. These 2 agents, when either 0.004-0.006 mg/kg glycopyrrolate or 0.03-0.06 mg/kg propantheline bromide was added to them produced rapid and permanent **reversal** of the **pancuronium** produced **neuromuscular block** with minimal fluctuations in heart rate and with almost no incidence of arrhythmias. In the case of over curarization no known **reversing** regimen is fully effective in the therapeutically safe dose range.

L36 ANSWER 24 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1974:22842 CAPLUS
DOCUMENT NUMBER: 80:22842
TITLE: Galanthamine versus neostigmine for **reversal** of nondepolarizing **neuromuscular block** in man
AUTHOR(S): Baraka, Anis; Cozanitis, Demetri
CORPORATE SOURCE: Dep. Anesthesiol., American Univ. Beirut, Beirut, Lebanon
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (1973), 52(5), 832-6
CODEN: AACRAT; ISSN: 0003-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In anesthetized adults, **pancuronium** (I) [15500-66-0] and d-**tubocurarine** [57-94-3] were equipotent **neuromuscular** blocking agents in doses of 0.03 and 0.15 mg/kg, resp. **Neuromuscular** blocking by either agent could be **reversed** by galanthamine-HBr [1953-04-4] or neostigmine [59-99-4] in doses of 0.3 and 0.015 mg/kg, resp.

L36 ANSWER 25 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1969:479450 CAPLUS
DOCUMENT NUMBER: 71:79450
TITLE: Neomycin-curare **neuromuscular block** and **reversal** in cats
AUTHOR(S): Stanley, Vayden F.; Giesecke, A. H., Jr.; Jenkins, Marion Tohomas
CORPORATE SOURCE: Southwestern Med. Sch., Univ. of Texas, Dallas, TX, USA
SOURCE: Anesthesiology (1969), 31(3), 228-32
CODEN: ANESAV; ISSN: 0003-3022
DOCUMENT TYPE: Journal
LANGUAGE: English

AB d-**Tubocurarine** was 100 times more potent than neomycin in producing **neuromuscular block** in a cat sciatic nerve-gastrocnemius muscle prepn.; 0.1 mg. d-tubocurarine/kg. or 10 mg. neomycin/kg. was necessary to depress the twitch response by 40%. The 2 drugs in combination were synergistic at doses causing >30% depression of the twitch response. Recovery from complete neomycin paralysis required 30-40 min. and was accelerated by the administration of 0.37 meq. Ca2+/kg. Neostigmine was less effective in accelerating recovery. The combination of 0.1 meq. Ca2+ and 1 meq. NaHCO3/kg. effectively **reversed** neomycin paralysis.

L36 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1958:41803 CAPLUS
DOCUMENT NUMBER: 52:41803
ORIGINAL REFERENCE NO.: 52:7533i,7534a
TITLE: **Reversal** by oximes of **neuromuscular block** produced by anticholinesterases
AUTHOR(S): Holmes, R.; Robins, E. L.
CORPORATE SOURCE: Chem. Defence Exptl. Estab., Porton, UK
SOURCE: British Journal of Pharmacology and Chemotherapy (1955), 10, 490-5
CODEN: BJPCAL; ISSN: 0366-0826
DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB Wedensky block in the isolated rat phrenic nerve-diaphragm prepn. induced by tetraethyl pyrophosphate (I), diisopropyl phosphorofluoridate (II), or sarin was rapidly reversed by diisonitrosoacetone and monoisonitrosoacetone. Pyridine-2-aldoxime methiodide reversed block due to anticholinesterases and itself caused neuromuscular block at higher concns. In rat gracilis muscle in vivo, II caused an increase in conduction velocity, which was restored to normal by oximes. Block in the cat tibialis muscle due to intravenous I or sarin was slowly reversed by oximes. The oximes did not reverse block caused by d-tubocurarine, succinylcholine, or decamethonium, and they had a direct toxic action on muscle.

L42 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:353267 CAPLUS
DOCUMENT NUMBER: 136:363859
TITLE: Use of cortisol-sequestering agents for the treatment of hypercortisolemia-related disorders
INVENTOR(S): Zhang, Mingquiang; Hill, David Robert; Rees, David
PATENT ASSIGNEE(S): Akzo Nobel N.V., USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036105	A2	20020510	WO 2001-EP12267	20011030
WO 2002036105	A3	20021031		
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002020654	A5	20020515	AU 2002-20654	20011030
EP 1333842	A2	20030813	EP 2001-992568	20011030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: EP 2000-309725 A 20001102
WO 2001-EP12267 W 20011030

AB The invention relates to the use of sequestering agents for the prepn. of a medicament for the treatment of hypercortisolemia-related disorders, esp. for the treatment of major depression; to pharmaceutical compns. comprising a cortisol-sequestering agent, and to the cortisol-sequestering agent 6-per-deoxy-6-per-(2,3-dihydroxypropylthio)-.gamma.-**cyclodextrin**.

L42 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:251270 CAPLUS
DOCUMENT NUMBER: 137:226182
TITLE: 2-O-Substituted **Cyclodextrins** as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide
AUTHOR(S): Tarver, Gary J.; Grove, Simon J. A.; Buchanan, Kirsteen; **Bom, Anton**; Cooke, Andrew; Rutherford, Samantha J.; Zhang, Ming-Qiang
CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd., Newhouse, Lanarkshire, ML1 5SH, UK
SOURCE: Bioorganic & Medicinal Chemistry (2002), 10(6), 1819-1827
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of secondary face modified **cyclodextrins** (CDs) were synthesized with the aim of constructing host mols. capable of forming host-guest complexes with neuromuscular blockers, esp. with rocuronium bromide. Perfacial 2-O-substitution of .gamma.-CD with 4-carboxybenzyl resulted in a CD host mol. 1 that forms a 1:1 binary complex with rocuronium bromide (Ka 6.2.times.105 M-1). The biol. activities of this compd. and other derivs. as reversal agents of rocuronium bromide were examd. in vitro (mouse hemi-diaphragm) and in vivo (anesthetized guinea pigs). The host mol. 1 was found to exert potent reversal activity (ED50 0.21 .mu.mol/kg, iv) against rocuronium-induced neuromuscular block, and thus proved the viability of using host mols. as antidotes of a biol. active compd.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:212211 CAPLUS
DOCUMENT NUMBER: 136:386312
TITLE: **Cyclodextrin**-Derived Host Molecules as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide: Synthesis and Structure-Activity

Relationships
AUTHOR(S): Adam, Julia M.; Bennett, D. Jonathan; Bom, Anton; Clark, John K.; Feilden, Helen; Hutchinson, Edward J.; Palin, Ronald; Prosser, Alan; Rees, David C.; Rosair, Georgina M.; Stevenson, Donald; Tarver, Gary J.; Zhang, Ming-Qiang
CORPORATE SOURCE: Departments of Medicinal Chemistry and Pharmacology, Organon Laboratories Ltd., Newhouse, ML1 5SH, UK
SOURCE: Journal of Medicinal Chemistry (2002), 45(9), 1806-1816
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of mono- and per-6-substituted cyclodextrin derivs. were synthesized as synthetic receptors (or host mols.) of rocuronium bromide, the most widely used neuromuscular blocker in anesthesia. By forming host-guest complexes with rocuronium, these cyclodextrin derivs. reverse the muscle relaxation induced by rocuronium in vitro and in vivo and therefore can be used as reversal agents of the neuromuscular blocker to assist rapid recovery of patients after surgery. Because this supramol. mechanism of action does not involve direct interaction with the cholinergic system, the reversal by these compds. is not accompanied by cardiovascular side effects usually attendant with acetylcholinesterase inhibitors such as neostigmine. The structure-activity relationships are consistent with this supramol. mechanism of action and are discussed herein. These include the effects of binding cavity size and hydrophobic and electrostatic interaction on the reversal activities of these compds.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:108136 CAPLUS
DOCUMENT NUMBER: 137:588
TITLE: A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host
AUTHOR(S): Bom, Anton; Bradley, Mark; Cameron, Ken; Clark, John K.; Van Egmond, Jan; Feilden, Helen; MacLean, Elizabeth J.; Muir, Alan W.; Palin, Ronald; Rees, David C.; Zhang, Ming-Qiang
CORPORATE SOURCE: Departments of Medicinal Chemistry, Pharmacology, Organon Laboratories Ltd., Newhouse, ML1 5SH, UK
SOURCE: Angewandte Chemie, International Edition (2002), 41(2), 265-270
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A cyclodextrin (CD)-based synthetic receptor of rocuronium bromide, a neuromuscular blocker (NMB) in anesthesia, was developed. This per-6-deoxy-per-6-sulfanyl-.gamma.-CD deriv., Org25969, has high affinity as revealed by isothermal titrn. calorimetry and x-ray crystallog. data. Org25969 was shown to reverse the NMB effect of rocuronium bromide in vitro (mouse hemi-diaphragm) and in vivo (anesthetized monkeys). The reversal of this biol. activity was possibly mediated by chem. encapsulation of the blocker, which is a novel therapeutic approach. This synthetic CD and its supramol. mechanism of action appeared to be superior to currently clin. used reversal agents in terms of speed and side effects.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:640126 CAPLUS
TITLE: Chemical chelation as a novel method of NMB reversal: Discovery of a synthetic cyclodextrin Org 25969
AUTHOR(S): Zhang, Ming-Qiang; Bom, Anton; Cameron, Kenneth S.; Clark, John K.; Feilden, Helen; Hutchinson, Edward; Muir, Alan W.; Palin, Ronald; Rees, David C.
CORPORATE SOURCE: Department of Medicinal Chemistry, Organon Laboratories Ltd, Lanarkshire, N/A, UK
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-307. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB We hypothesized that chem. chelation of neuromuscular blockers (NMBAs) by an exogenous host mol. such as **cyclodextrins** would promote the dissocn. of NMBAs from their site of action, i.e., nAChR on the muscle, leading to the reversal of neuromuscular blockade. Since this mechanism of action does not involve direct activation of cholinergic systems, it may circumvent the undesired side-effects attendant with AChE inhibitors such as neostigmine. It has also the potential advantage to be used for the reversal of both depolarizing and non-depolarizing NMBAs, because of this lack of involvement of nAChRs in the mechanism of action. In addn., the chelators may further be safely employed for the reversal of -profound (or complete) block'. In this presentation we shall describe the discovery of Org 25969, a synthetic **cyclodextrin**-based host mol. that forms tight host-guest complex with rocuronium and as a result reverses rocuronium-induced neuromuscular block. The reversal produced by Org 25969 is not only fast and highly efficient, but also without any visible CV side-effects. The designed synthesis of this NCE as well as its complexation thermodn. with rocuronium will be discussed.

L42 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:137035 CAPLUS
DOCUMENT NUMBER: 134:193457
TITLE: Use of chemical chelators as reversal agents for drug-induced neuromuscular block
INVENTOR(S): **Bom, Antonius Helena Adolf**; Muir, Alan William; Rees, David
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012202	A2	20010222	WO 2000-EP7694	20000807
WO 2001012202	A3	20011115		
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013126	A	20020423	BR 2000-13126	20000807
EP 1210090	A2	20020605	EP 2000-964006	20000807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507335	T2	20030225	JP 2001-516547	20000807

PRIORITY APPLN. INFO.: EP 1999-306411 A 19990813
WO 2000-EP7694 W 20000807

OTHER SOURCE(S): MARPAT 134:193457

AB Cyclophanes I [R = (CH2)5, 4-CH2C6H4CH2, 1,4-cyclohexanediyldimethylene; n = 1, 2, 3] and II [X = (CH2)5, 4-CH2C6H4CH2, 2,6-naphthalenediyldimethylene] were prepd. Thus, the tetra-Me ester of I [R = (CH2)5, n = 2] was prepd. from 1,7,21,27-tetraaza[7.1.7.1]paracyclophane and 3-(methoxycarbonyl)propionyl chloride and was sapond. to give the tetracarboxylic acid. Both in vivo tests of **cyclodextrin** derivs. and in vitro tests of I, II, and **cyclodextrin** derivs. as reversal agents for drug-induced neuromuscular block were described.

L42 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:765783 CAPLUS
DOCUMENT NUMBER: 132:54637
TITLE: A review of recent applications of **cyclodextrins** for drug discovery
AUTHOR(S): Zhang, Ming-Qiang; **Rees, David C.**
CORPORATE SOURCE: Medicinal Chemistry Department, Organon Laboratories, Newhouse, ML1 5SH, UK
SOURCE: Expert Opinion on Therapeutic Patents (1999), 9(12), 1697-1717
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB This review, with 62 refs., summarizes the pharmaceutical applications of **cyclodextrins** (CDs), particularly including the patent literature 1996-1999. To place these developments in context there is an introduction to the previously reported mol. and supramol. (complex

formation) properties of CDs and their biol. properties, and clin. applications, which mainly involve drug (re)formulation. The growing utility of CDs as pharmaceutical excipients is discussed in three main categories. Firstly, complexes formed between CDs and previously known drugs wherein the new conjugate confers improved efficacy or reduced side effects. Secondly, conjugates conferring improved aq. soly. and thirdly, a misc. category including conjugates with new compds. In addn., the emerging areas of covalently bound CD-drug complexes and potential applications of CDs acting directly as medicinal agents in their own right are reviewed. In some of these applications chem. modified CDs are found to augment the patentability and properties of the well known .alpha.-, .beta.- and .gamma.-CDs. The chem. structures of these novel CDs are discussed together with the challenge of their synthesis and purifn. During the period covered by this review the no. of patents and publications describing therapeutic applications of CDs has continued to grow while the industrial prodn. of this fascinating class of supramol. compds. has increased substantially leading to a corresponding fall in price.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:637764 CAPLUS

DOCUMENT NUMBER: 131:321427

TITLE: Apolipoprotein A-I stimulates secretion of apolipoprotein E by foam cell macrophages

AUTHOR(S): **Rees, David**; Sloane, Timothy; Jessup, Wendy; Dean, Roger T.; Kritharides, Leonard

CORPORATE SOURCE: Cell Biology, Heart Research Institute, Sydney, 2050, Australia

SOURCE: Journal of Biological Chemistry (1999), 274(39), 27925-27933
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Apolipoprotein A-I (apoA-I) overexpression inhibits atherogenesis in mice, and apolipoprotein E (apoE) secreted by foam cell macrophages may exert antiatherogenic effects within the arterial wall. We hypothesized that interaction between apoA-I and apoE contributed to the antiatherogenic properties of apoA-I, and therefore investigated whether apoA-I stimulated secretion of apoE by foam cell macrophages. Cholesterol enrichment of primary murine and human macrophages increased spontaneous apoE secretion 2-fold, as quantified by Western blot and chemiluminescence detection. Human apoA-I caused a further marked increase of apoE secretion from both murine (3.8-fold, $p < 0.01$) and human (3.2-fold, $p = 0.01$) foam cells in a time- and concn.- dependent manner, and this increase was confirmed by immunopptn. of [35S]methionine-labeled macrophage apoE. The protein synthesis inhibitor cycloheximide, but not the transcription inhibitor actinomycin D, markedly inhibited apoE secretion to apoA-I (73.1 .+-. 9.8% inhibition at 4 h) and completely suppressed apoE secretion beyond 4 h. Pretreatment of macrophages with Pronase inhibited initial apoA-I-mediated apoE secretion by 70.5 .+-. 6.5% at 2 h, but by 8 h apoA-I-induced apoE secretion was the same in Pronase-pretreated and non-pretreated cells. Non-apolipoprotein-mediated cholesterol efflux induced by trimethyl-.beta.-**cyclodextrin** did not enhance apoE secretion, whereas phospholipid vesicles inducing the same degree of cholesterol efflux substantially enhanced apoE secretion, and apoA-I and phospholipid vesicles in combination demonstrated additive induction of apoE secretion. We conclude that apoA-I concurrently stimulates apoE secretion and cholesterol efflux from foam cell macrophages and that lipoprotein-derived apoA-I may enhance local secretion and accumulation of apoE in atherosclerotic lesions.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT